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Total serum testosterone and WOMAC pain and function among older men and women with severe knee OA

Freystaetter, Gregor ; Fischer, Karina ; Orav, Endel J ; Egli, Andreas ; Theiler, Robert ; Münzer, Thomas ; Felson, David T ; Bischoff-Ferrari, Heike A

Abstract: OBJECTIVES: We investigated if serum total testosterone (T)-level is associated with knee pain and function in men and women with severe knee osteoarthritis (OA). METHODS: We enrolled 272 adults 60 years (70.4 ± 4.4 years, 53% women) who underwent unilateral total knee replacement (TKR) due to severe knee OA. Serum T-levels and WOMAC pain and function of the operated and contralateral knee were measured at 6-8 weeks after surgery. At the non-operated knee, 56% participants had radiographic knee OA with a Kellgren-Lawrence grade 2. Cross-sectional analyses were performed by gender and BMI subgroups using multivariable regression adjusted for age, physical activity and BMI. RESULTS: At the operated knee, higher T-levels were associated with less WOMAC pain in men ($B = -0.62$; $P = 0.046$) and women ($B = -3.79$; $P = 0.02$), and less WOMAC disability scores in women ($B = -3.62$; $P = 0.02$) and obese men ($B = -1.99$; $P = 0.02$). At the non-operated knee, T-levels were not associated with WOMAC pain in men or women, but higher T-levels were associated with less disability in women ($B = -0.95$; $P = 0.02$). T-levels were inconsistently associated with pain and disability in BMI subgroups among men. Only among obese women, T-levels were inversely associated with radiographic knee OA ($OR = 0.10$; $P = 0.003$). CONCLUSIONS: Higher total T-levels were associated with less pain in the operated knee in men and women undergoing TKR and less disability in women. At the non-operated knee, higher T-levels were inconsistently associated with less pain and disability.

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10 **Total serum testosterone and WOMAC pain and function among older men and women**
11 **with severe knee OA**

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42 **ABSTRACT**

43 **Objectives:** We investigated if serum total testosterone (T)-level is associated with knee pain and
44 function in men and women with severe knee osteoarthritis (OA).

45 **Methods:** We enrolled 272 adults ≥ 60 years (70.4 ± 4.4 years, 53% women) who underwent
46 unilateral total knee replacement (TKR) due to severe knee OA. Serum T-levels and WOMAC
47 pain and function of the operated and contra-lateral knee were measured at 6-8 weeks after
48 surgery. At the non-operated knee, 56% participants had radiographic knee OA with a Kellgren-
49 Lawrence grade ≥ 2 . Cross-sectional analyses were performed by gender and BMI subgroups using
50 multivariable regression adjusted for age, physical activity and BMI.

51 **Results:** At the operated knee, higher T-levels were associated with less WOMAC pain in men (B
52 $= -0.62$; $P = 0.046$) and women ($B = -3.79$; $P = 0.02$), and less WOMAC disability scores in
53 women ($B = -3.62$; $P = 0.02$) and obese men ($B = -1.99$; $P = 0.02$). At the non-operated knee, T-
54 levels were not associated with WOMAC pain in men or women, but higher T-levels were
55 associated with less disability in women ($B = -0.95$; $P = 0.02$). T-levels were inconsistently
56 associated with pain and disability in BMI subgroups among men. Only among obese women, T-
57 levels were inversely associated with radiographic knee OA ($OR = 0.10$; $P = 0.003$).

58 **Conclusions:** Higher total T-levels were associated with less pain in the operated knee in men and
59 women undergoing TKR and less disability in women. At the non-operated knee, higher T-levels
60 were inconsistently associated with less pain and disability.

61

62 Significance & Innovation

- 63 • Among both men and women with severe knee osteoarthritis who underwent unilateral
64 total knee replacement, higher serum testosterone levels were associated with less
65 WOMAC pain in the operated knee, independent of age, BMI and physical activity.
- 66 • Among women but not men, higher serum testosterone levels were also associated with
67 less WOMAC disability in the operated and the non-operated knee, independent of age,
68 BMI and physical activity.

72 INTRODUCTION

73 Knee osteoarthritis (OA) is the most common cause of difficulty walking in older adults (1).
74 Thirty percent of adults will develop symptomatic knee OA by the age of 65 and nearly 50 percent
75 of adults will develop symptomatic knee OA by the age of 85 years, with the highest risk among
76 those who were overweight during extended periods of their lifetime (2).

77 Prevalence of symptomatic knee OA increases similarly with age in women and men until the age
78 of 50. In the second half of life, women have a significantly higher prevalence of symptomatic
79 knee OA (3) and greater disability from knee OA than men (4, 5). The gender difference in knee
80 OA prevalence and severity in the second half of life has not been well understood (4, 6).
81 However, given that cells in knee articular cartilage, underlying bone and surrounding muscles in
82 men and women, express receptors for both estrogen and testosterone (T) (7, 8), it is likely that
83 hormonal factors are involved (4, 6) with a potential benefit of a greater physiological T-exposure
84 (7, 9-11).

85 With regard to changes in T-exposure with age, T-levels have been shown to decrease by
86 approximately 1% per year in men starting at age 40 (12). Clinical signs of T-deficiency in older
87 men are a decrease in muscle mass and strength, a decrease in bone mass and an increase in
88 central body fat (13). Women have 20-fold lower T-levels compared to men (14), and their T-
89 levels also decline with age reaching a nadir after menopause with a decline close to 15% of their
90 premenopausal stage (15). Although the biological role of T in women remains unclear, the sharp
91 and rapid decline after menopause may contribute to the age-related decline in physical function
92 among women (7, 9-11, 16).

93 With regard to studies that link T-levels to OA, lower serum T-levels have been associated with a
94 higher prevalence of hand but not knee OA in one study (17). Further, a small cross-sectional
95 study among 45 healthy middle-aged men suggested a positive association between higher serum
96 T-levels and medial tibial cartilage thickness (9). In one larger study of 309 overweight adults age
97 60 years and older with knee OA, higher T-levels were found to be associated with less WOMAC
98 stiffness among men and better WOMAC function among women (18).

99 With regard to pain sensitivity and potential relevance to OA, clinical and experimental
100 investigations have consistently shown gender-specific differences for both pain sensitivity and

threshold (19). Although the underlying mechanisms for these differences are not well understood, an influence of T on nociceptive processing is well established (19, 20). In fact, it has been suggested that T protects men from chronic musculoskeletal pain conditions (21), either by a direct effect on nociceptive processing (19, 20), or indirectly by an increase in muscle mass, strength, and function as suggested by two clinical trials with T-treatment among frail and hypogonadal older men (22, 23). Further potential benefits of higher physiological T-levels on OA pain and function may be explained by prior data that linked higher T-exposure to a decrease in fat mass and inflammatory response among men (7, 9-11). Further, preoperative supra-physiological T-administration has been suggested to confer some early functional benefit among older men undergoing knee replacement in a small study of 25 men (24).

The aim of this cross-sectional study was to investigate a possible association between total serum T-levels and symptoms of knee OA with regard to pain and disability in the operated and non-operated knee among men and women age 60 years and older, who underwent unilateral total knee replacement (TKR) due to severe knee OA 6 to 8 weeks earlier. We chose this target population given their high risk of OA at the contra-lateral non-operated knee (25, 26) as well as the potential shared benefits of higher physiological T-levels on pain and disability at the operated and non-operated knee.

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120 PATIENTS AND METHODS

121 Study design and Participants

The present study is a cross-sectional analysis of the baseline data from the Zurich Multiple Endpoint Vitamin D Trial in Knee OA Patients (NCT00599807; clinicaltrials.gov) (27). The original study was a 2-year double blind randomized controlled trial that investigated the effect of Vitamin D (2000 vs. 800 IU/d cholecalciferol) on pain and disability related to the rehabilitation of the operated knee and contra-lateral knee among 273 seniors age 60 years and older (mean age 70.3 years, 53% women) who underwent elective surgery for unilateral TKR due to severe knee OA. The baseline assessment took place 6-8 weeks after surgery at the Centre on Aging and Mobility at the University of Zurich, Switzerland, from October 2007 to February 2013. In the

original trial, participants were not selected based on their vitamin D status and 31.4% of participants were vitamin D deficient at baseline (27). Of 273 participants enrolled, one male participant was excluded due to missing data on serum T-concentration reducing the analytical sample size for this study to 272 (for the radiologic assessment data was only available for 270 participants). Exclusion criteria of the original trial were history of inflammatory arthritis, chronic corticosteroid use, history of malabsorption disorder, kidney disease (estimated creatinine clearance <30 mL/min), current cancer, treatment with bisphosphonate, PTH hormone therapy, calcitonin therapy in the 6 months prior to enrolment, severe cognitive/visual/hearing impairments, inability to walk at least 3 meters with or without a walking aid (27). All participants gave their written informed consent and the study was approved by the Cantonal Ethical Commission of Zurich (Protocol identifier STZ 20/07), Switzerland.

141

142 **Measurement of serum T-concentration**

143 Fasting blood samples were taken between 8:00 and 9:30 am. Serum concentration of total T was
144 measured by an electrochemoluminescence immunoassay (Roche Diagnostics, Rotkreuz,
145 Switzerland) with an inter-assay coefficient of variation (CV) of 3.9% at a level of 7.3 nmol/L and
146 3.5% at a level of 18.8 nmol/L.

147

148 **Assessment of covariates**

149 Body mass index (BMI, in kg/m^2) was calculated as weight divided by height squared. BMI
150 categories were defined according to WHO guidelines as underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$),
151 normal weight ($\text{BMI} \geq 18.5$ and $< 25 \text{ kg/m}^2$), overweight ($\text{BMI} \geq 25$ and $< 30 \text{ kg/m}^2$), and obese
152 ($\geq 30 \text{ kg/m}^2$).

153 Physical activity levels were measured by an ankle-worn ambulatory activity monitor
154 (StepWatch™ Step Activity Monitor, Cyma, Seattle, WA), which records the number of steps
155 taken every minute. The StepWatch monitor has been validated for use in older adults (28) and has
156 been used to monitor physical activity in several patient groups including patients with knee OA
157 (29). In the current study, participants were instructed to wear the monitor during the day for
158 seven consecutive days. A measurement was considered as valid if at least three days with ≥ 10

hours of recording were available, omitting blocks of >180 minutes of consecutive zeros, which was interpreted as device not worn. Minutes spent on moderate to vigorous physical activity (MVPA) were defined as the average minutes per day with ≥ 30 steps/min according to the manufacturer's software manual (StepWatch™ 3.1 Software Manual).

163

164 Outcome measurements

165 *Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function*
166 *score*

167 Knee pain and function (disability) of the operated and the non-operated knee were assessed by
168 the respective subscales of the WOMAC questionnaire. The WOMAC is a broadly validated and
169 commonly used self-reported outcome tool for knee OA (30), including patients undergoing knee
170 replacement (31). It consists of 24 items divided into 3 subscales: pain (5 items), stiffness (2
171 items) and physical function (17 items), with each item scoring on a 5-point Likert scale (none,
172 mild, moderate, severe, and extreme). For the pain and physical function subscale, these scores
173 were transformed to a 0 to 100 score (0 = no symptoms, 100 = extreme symptoms) with higher
174 scores indicating more pain and more disability. We used a knee-specific paper-version of the
175 German WOMAC 3.1 (32).

176

177 *Radiologic Assessment of knee osteoarthritis at the non-operated knee*

178 To rate knee OA at the non-operated knee, we performed a plain x-ray of the contra-lateral knee in
179 a semi-flexed weight-bearing position (we used the Multicentre Osteoarthritis Study (MOST)
180 study centre standardized X-ray assessment procedures (33)). Kellgren-Lawrence (KL) grades
181 were classified by a blinded knee OA radiology expert (0 = no radiographic features of
182 osteoarthritis; 1 = possible joint space narrowing and osteophyte formation; 2 = definite
183 osteophyte formation with possible joint space narrowing; 3 = multiple osteophytes, definite joint
184 space narrowing, sclerosis and possible bony deformity; 4 = large osteophytes, marked joint space
185 narrowing, severe sclerosis and definite bone deformity) (34).

186

187 **Statistical analysis**

188 Statistical analysis was performed using SAS version 9.4 (SAS Institute, Inc., Cary, North
189 Carolina, USA). Distributions of continuous variables were examined for normality. Differences
190 in baseline characteristics between men and women were analyzed by using a χ^2 test for
191 categorical variables and a Student's *t* test for continuous variables.

192 Associations between serum T-concentration and WOMAC pain and function (disability) score
193 were analyzed by using multivariable robust linear regression models. For these analyses, among
194 women only, T-levels were natural logarithmically (ln) transformed to approach normality. At the
195 non-operated knee only, we also assessed the association between T-levels and KL grades based
196 on ordinal logistic regression models. All analyses were performed in an unadjusted way (Model
197 1) and adjusted for age, BMI status (normal weight, overweight, obese; except in BMI strata), and
198 physical activity (Model 2); and for men and women separately. For all analyses Model 2 was
199 considered the main model. Moreover, we performed subgroup analysis by BMI (normal weight,
200 overweight, and obese) to investigate whether specific BMI subgroups of seniors are more
201 sensitive with regard to the relation between T and WOMAC scores or KL grades. These analyses
202 were performed because obesity is a very well documented risk factor for knee OA (35, 36) and
203 several studies have shown that T-levels are inversely associated with BMI (37, 38).

204 Statistical significance was set at $P \leq 0.05$; reported *P* values are two-sided.

205

206

207 **RESULTS**

208 The characteristics of the 272 study participants (127 men and 145 women) are shown in Table 1.
209 There were no significant differences between men and women with regard to mean age, BMI,
210 and KL grades. Women were significantly less physically active and had lower serum T-levels
211 than men. Moreover, women had significantly worse (higher) WOMAC pain and more disability
212 (higher WOMAC function scores) at the operated knee and worse disability (higher WOMAC
213 function scores) at the non-operated knee compared with men. At the non-operated knee, 48.4%
214 (61/126) of men and 61.6% (90/144) of women had KL grade 2 or higher consistent with
215 radiographic knee OA.

216 In multivariable-adjusted analyses, at the operated knee (Table 2, Model 2), higher T-levels were
217 associated with less WOMAC pain in both men ($B = -0.62$; 95% CI: -1.23, -0.01; $P = 0.05$) and
218 women ($B = -3.79$; 95% CI: -6.90, -0.69; $P = 0.02$). This association was most pronounced in the
219 subgroup of normal-weight men ($B = -1.16$; 95% CI: -2.17, -0.15; $P = 0.02$) as well as in the
220 subgroup of normal-weight women ($B = -9.27$; 95% CI: -15.56, -2.98; $P = 0.004$). At the operated
221 knee, higher T-levels were also associated with less disability among obese men ($B = -1.99$; 95%
222 CI: -3.62, -0.37; $P = 0.02$) and less disability among all women ($B = -3.62$; 95% CI: -6.65, -0.58;
223 $P = 0.02$), and most pronounced among normal-weight women ($B = -6.54$; 95% CI: -12.81, -0.28;
224 $P = 0.04$).

225 At the non-operated knee (Table 2), higher T-levels were associated with less WOMAC pain only
226 in normal-weight men ($B = -0.39$; 95% CI: -0.68, -0.10; $P = 0.009$). Further, at the non-operated
227 knee, higher T-levels were associated with less disability (better WOMAC function), among all
228 women ($B = -0.95$; 95% CI: -1.73, -0.17; $P = 0.02$). With regard to the association between T-
229 level and KL-grade, only among obese women (Table 3), per one nmol/L increase in T-level, the
230 odds of a higher KL-grade was reduced 10-fold ($OR = 0.10$; 95% CI: 0.02, 0.45; $P = 0.003$).

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232

233

234 DISCUSSION

235 In this cross-sectional study among 272 men and women with severe knee OA who underwent
236 unilateral TKR 6 to 8 weeks prior to enrolment, we found an association of T-level with symptoms
237 of OA in the operated and the non-operated knee. Specifically, among both men and women,
238 higher serum T-levels were associated with less WOMAC pain in the operated knee. Further,
239 among women but not men, higher serum T-levels were also associated with less WOMAC
240 disability in the operated and the non-operated knee. Notably, these associations were independent
241 of age, BMI, and physical activity. With regard to subgroups by BMI, there were inconsistent
242 signals for men in the non-operated knee. Further, only among obese women, higher T-levels were
243 associated with less radiographic changes due to knee OA. Consistent with the literature (25, 26),

244 48% of men and 42% of women had radiographic knee OA at the non-operated knee according to
245 standardized x-rays performed in all participants.

246 Our findings are consistent with an earlier study describing a non-significant inverse association
247 between T-level and WOMAC disability among women and WOMAC stiffness among men with
248 symptomatic knee OA age 60 years and older (18). As outlined in the introduction of this
249 manuscript, a potential benefit of T-level with regard to pain and disability among patients with
250 severe knee OA could be explained by prior findings supporting a positive association of higher T-
251 levels with better muscle strength (39, 40) and better muscle function (41) in patients with knee
252 OA. Further, an influence of T on nociceptive processing (19, 20) and inflammatory response has
253 been suggested in several studies (7, 9-11), all of which are considered important pathways in the
254 development of OA (42, 43).

255 Except among obese women, we did not find an association between T-levels and radiographic
256 changes of knee OA despite the high prevalence of radiographic OA at the non-operated knee in
257 our study. On the one hand, this is in line with prior studies where symptoms and the extent of
258 radiographic changes show discrepant findings (36, 44). On the other hand, we may have missed
259 such an association due to the sample selection, where the most severely affected knee had
260 undergone surgery and could not be assessed radiographically with respect to KL grade. Notably,
261 however, symptoms are considered the patient-relevant feature of OA rather than the extent of
262 radiographic changes (45).

263 Our study has several strengths. The results for the association of T levels and pain are consistent
264 for men and women at the operated knee, and disability for women at the operated and non-
265 operated knee. Also, our study has a moderately large sample size with 272 men and women age
266 60 years and older. Further, we used the WOMAC questionnaire considered the gold standard for
267 pain and disability measurement among patients with knee OA with and without TKR (31, 46).
268 Finally, WOMAC scores of our study are representative of those reported in the literature among
269 similar patient groups (47, 48).

270 Our study also has limitations. Its cross-sectional design does not allow the exploration of cause
271 and effect. Also, our study is a secondary analysis of a randomized controlled trial not powered for
272 the association of T-level and symptoms of knee OA. Therefore, it is possible that the study was
273 underpowered to show significant results for all subgroups. Further, assessments were obtained 6

274 to 8 weeks after unilateral TKR. Thus, it is possible that analgesic regimens, and especially the use
275 of opioid pain medications (49), may have influenced the association between T-levels and
276 WOMAC pain and disability. Notably, in one large cross-sectional study (NHANES) (50),
277 participants on opioids had a higher odds of having low T-levels than those unexposed to opioids,
278 which is consistent with further literature suggesting that opioids can suppress gonadal hormone
279 production possibly reducing T-levels (49). Unfortunately, we were not able to explore the
280 potential confounding by use of pain medication (and specifically opioid use) on pain and
281 disability in our study. However, all participants were recruited in a stable health state, 6 to 8
282 weeks after surgery with rehabilitation efforts largely completed, and thereby reduced likelihood
283 of exposure to opioid pain medications.

284 In summary, the present study suggests a possible advantage of higher gender-specific
285 physiological T-levels among both men and women undergoing unilateral TKR due to severe knee
286 OA. Additional studies with a prospective design are needed to further explore and clarify the role
287 of higher physiological T-levels in patients with symptomatic knee OA.

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TABLES

TABLE 1

Characteristics of participants of the Zurich Knee Osteoarthritis trial by gender

	Men	Women	Gender difference (<i>P</i>)	Total population
Subjects [n (%)]	126 (47)	146 (53)	0.25	272
Age a (y)	70.3 (6.9)	70.4 (6.0)	0.83	70.4 (6.4)
Body mass index (kg/m ²)	27.6 (3.8)	26.9 (4.1)	0.11	27.2 (3.9)
Physical activity (min MVPA/day)	45.3 (23.4)	37.9 (21.6)	0.009	42.3 (22.6)
Total testosterone (nmol/L)	13.0 (4.6)	0.4 (0.4)	<0.0001	6.3 (7.0)
Kellgren-Lawrence grade [<i>n</i> (%)] ^a				
0	32 (56)	25 (44)	0.11	57 (21)
1	33 (53)	29 (47)		62 (23)
2	18 (33)	36 (67)		54 (20)
3	31 (42)	42 (58)		73 (27)
4	12 (50)	12 (50)		24 (9)
WOMAC pain score (0-100)				

Operated knee	23.9 (14.4)	32.6 (14.4)	<0.0001	28.5 (15.0)
Non-operated knee	4.2 (8.1)	5.2 (8.2)	0.32	4.7 (8.1)
WOMAC functional score (0-100)				
Operated knee	21.8 (12.6)	29.2 (13.9)	<0.0001	25.8 (13.8)
Non-operated knee	2.9 (6.6)	5.4 (8.9)	0.01	4.3 (8.0)

Data are crude means (\pm SD) or n (%). Differences between men and women were assessed by using Student's t test for continuous variables and a χ^2 test for categorical variables. P values are two-sided; statistical significance is set at $P < 0.05$. Abbreviations: MVPA, moderate to vigorous physical activity; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

^a Values refer to the non-operated knee ($n = 270$).

TABLE 2

Cross-sectional association between blood total testosterone concentration and Western Ontario and McMaster Universities Arthritis Index (WOMAC) post-operative pain and functional scores in seniors age 60 and older with knee osteoarthritis by gender

	Men				Women ^a			
	Model 1		Model 2		Model 1		Model 2	
	<i>B</i> (95% CI)	<i>P</i>	<i>B</i> (95% CI)	<i>P</i>	<i>B</i> (95% CI)	<i>P</i>	<i>B</i> (95% CI)	<i>P</i>
WOMAC pain score (0-100)								
Operated knee								
Total subjects (M/F)	-0.51 (-1.11, 0.09)	0.09	-0.62 (-1.23, -0.01)	0.05	-2.76 (-5.75, 0.23)	0.07	-3.79 (-6.90, -0.69)	0.02
Body mass index (kg/m ²)								
Normal weight (18.5-24.9) ^b	-1.25 (-2.23, -0.27)	0.013	-1.16 (-2.17, -0.15)	0.02	-5.67 (-11.81, 0.48)	0.07	-9.27 (-15.56, -2.98)	0.004
Overweight (25.0-29.9)	-0.08 (-0.87, 0.72)	0.85	-0.01 (-0.81, 0.80)	0.99	-3.54 (-7.75, 0.68)	0.10	-3.88 (-8.20, 0.43)	0.08
Obese (≥30.0)	-1.12 (-3.06, 0.82)	0.26	-1.36 (-3.54, 0.82)	0.22	0.28 (-5.07, 5.63)	0.92	1.30 (-3.62, 6.22)	0.60
<i>P</i> _{interaction}		0.29		0.38		0.09		0.01
Non-operated knee								

Total subjects (M/F)	-0.01 (-0.11, 0.08) 0.77	-0.07 (-0.17, 0.03) 0.20	0.52 (-0.23, 1.28) 0.18	0.42 (-0.55, 1.38) 0.39
Body mass index (kg/m ²)				
Normal weight (18.5-24.9) ^b	-0.27 (-0.54, 0.00) 0.050	-0.39 (-0.68, -0.10) 0.009	-0.08 (-1.10, 0.94) 0.88	0.05 (-1.43, 1.54) 0.94
Overweight (25.0-29.9)	0.0007 (-0.10, 0.10) 0.99	0.003 (-0.12, 0.13) 0.97	0.73 (-0.45, 1.91) 0.22	0.73 (-0.70, 2.16) 0.32
Obese (≥30.0)	-0.63 (-1.29, 0.03) 0.06	-0.33 (-0.90, 0.24) 0.25	-0.73 (-4.98, 3.53) 0.74	0.69 (-3.51, 4.90) 0.75
<i>P</i> _{interaction}	0.18	0.14	0.51	0.88
WOMAC functional score (0-100)				
Operated knee				
Total subjects (M/F)	-0.01 (-0.53, 0.51) 0.97	-0.11 (-0.66, 0.44) 0.70	-3.57 (-6.53, -0.61) 0.02	-3.62 (-6.65, -0.58) 0.02
Body mass index (kg/m ²)				
Normal weight (18.5-24.9) ^b	-0.62 (-1.67, 0.44) 0.25	-0.60 (-1.77, 0.56) 0.31	-6.51 (-12.34, -0.68) 0.03	-6.54 (-12.81, -0.28) 0.04
Overweight (25.0-29.9)	0.31 (-0.34, 0.95) 0.35	0.31 (-0.39, 1.00) 0.39	-3.41 (-7.29, 0.47) 0.09	-4.04 (-8.12, 0.04) 0.052
Obese (≥30.0)	-0.96 (-2.53, 0.61) 0.23	-1.99 (-3.62, -0.37) 0.02	-0.48 (-7.15, 6.20) 0.89	1.26 (-4.57, 7.08) 0.67
<i>P</i> _{interaction}	0.95	0.71	0.13	0.11
Non-operated knee				
Total subjects (M/F)	-0.0005 (-0.04, 0.03) 0.98	-0.0006 (-0.03, 0.03) 0.97	-0.66 (-1.33, 0.01) 0.05	-0.95 (-1.73, -0.17) 0.02

Body mass index (kg/m ²)								
Normal weight (18.5-24.9) ^b	0.04 (-0.32, 0.39)	0.83	0.02 (-0.25, 0.30)	0.88	0.07 (-0.62, 0.76)	0.85	0.05 (-0.82, 0.92)	0.91
Overweight (25.0-29.9)	0.004 (-0.01, 0.02)	0.64	-0.0006 (-0.20, 0.20)	0.87	-1.02 (-2.09, 0.04)	0.06	-1.24 (-2.49, 0.02)	0.054
Obese (≥30.0)	-0.07 (-0.28, 0.15)	0.55	0.001 (-0.02, 0.02)	0.99	-2.89 (-5.25, -0.53)	0.02	-2.50 (-5.14, 0.14)	0.06
$P_{\text{interaction}}$		0.35		0.16		0.17		0.13

Data (n = 272) are unstandardized regression coefficients (*B*) and 95% confidence intervals (95% CIs) for the association between blood total testosterone concentration (nmol/L) and WOMAC pain and functional scores derived from multivariable linear robust regression models unadjusted (Model 1) or adjusted for age, BMI status (normal weight, overweight, and obese; except BMI strata) and moderate to vigorous physical activity (Model 2) for men and women separately. *P* values are two-sided and uncorrected; statistical significance was set at $P \leq 0.05$. Abbreviations: BMI, body mass index; F, females; M, males; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

^a In women, the blood concentration of total testosterone was natural logarithmically (ln) transformed to approach normality.

^b One female senior was marginally underweight with BMI = 18.2.

TABLE 3

Cross-sectional association between blood total testosterone concentration and Kellgren-Lawrence grade in participants of the Zurich Knee Osteoarthritis trial stratified by gender ^a

	Men				Women			
	Model 1		Model 2		Model 1		Model 2	
	<i>OR</i> (95% CI)	<i>P</i>	<i>OR</i> (95% CI)	<i>P</i>	<i>OR</i> (95% CI)	<i>P</i>	<i>OR</i> (95% CI)	<i>P</i>
Kellgren-Lawrence grade (0-4)								
Total subjects (M/F)	1.01 (0.94, 1.08)	0.84	1.00 (0.93, 1.08)	0.90	0.54 (0.25, 1.19)	0.13	0.66 (0.29, 1.50)	0.32
Body mass index (kg/m ²)								
Normal weight (18.5-24.9) ^a	1.03 (0.90, 1.19)	0.67	0.99 (0.85, 1.15)	0.89	1.63 (0.23, 11.53)	0.62	2.85 (0.31, 26.32)	0.35
Overweight (25.0-29.9)	0.98 (0.89, 1.07)	0.59	0.99 (0.90, 1.08)	0.75	1.01 (0.30, 3.39)	0.99	0.94 (0.27, 3.26)	0.93
Obese (≥30.0)	1.10 (0.89, 1.38)	0.38	1.11 (0.87, 1.41)	0.39	0.21 (0.05, 0.87)	0.03	0.10 (0.02, 0.45)	0.003
<i>P</i> _{interaction}		0.54		0.72		0.11		0.06

Data (n = 270) are odds ratios (OR) and 95% confidence intervals (95% CIs) for the association between blood total testosterone concentration (nmol/L) and Kellgren-Lawrence grade derived from ordinal logistic regression models unadjusted (Model 1) or adjusted for age, BMI status (normal weight, overweight, obese; except BMI strata) and moderate to vigorous physical activity (Model 2) for men and women separately. *P* values are two-sided and uncorrected; statistical significance is set at $P \leq 0.05$. Bolded *P* values indicate a statistical significance at $P < 0.05$ level. Abbreviations: BMI, body mass index; F, females; M, males.

^aOne female senior was marginally underweight with BMI = 18.2 kg/m².